Exhibit C

Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study

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Summary

Background Hepatitis B and hepatitis C virus infections are common causes of death related to liver disease. In this large study, we aimed to investigate all cause mortality of the viruses in a community-based setting.

Methods In the study population, 39 109 people had hepatitis B, 75 834 had hepatitis C, and 2604 had hepatitis B and hepatitis C co-infection, notified to the New South Wales state health department, Australia, between 1990 and 2002. Their data were probabilistically linked to the National Death Index. Standardised mortality ratios for all causes of death were calculated and adjusted for age, sex, and calendar year.

Results The number of deaths identified by the linkage were 1233 (3·2 %) for hepatitis B, 4008 (5·3)% for hepatitis C, and 186 (7·1)% for hepatitis B and C co-infection. Raised risk of liver-related death (standardised mortality ratios 12·2, 95% CI 10·7–13·9; 16·8, 15·4–18·3, and 32·9, 23·1–46·7, for hepatitis B, hepatitis C, and hepatitis B and C co-infected patients, respectively) and drug-induced death (1·4, 1·0–2·0; 19·3, 18·1–20·5; and 24·7, 18·2–33·5, respectively) were detected. In people with hepatitis C, raised risk of dying from drug-related causes was significantly greater than from liver-related causes (p=0·012), with the greatest excess risk in women aged 15–24 years (56·9, 39·2–79·9).

Interpretation All groups had increased risk of liver-related death compared with the standard population, with the greatest excess in people diagnosed with hepatitis B and hepatitis C co-infection. Our data highlight that young people with hepatitis C and with co-infection face a higher mortality risk from continued drug use than from their infection, whereas the main cause of hepatitis B death was liver related.

Introduction

Chronic infection with hepatitis B or hepatitis C viruses are common causes of progressive liver disease, cirrhosis, and hepatocellular carcinoma.[1–4] Co-infection with hepatitis B and hepatitis C further increases risk of liver disease complications.[5] The natural history of hepatitis B and hepatitis C infections has been extensively studied, especially in relation to rates of progression of liver disease.[6,7] However, mortality related to hepatitis B and hepatitis C infection is less well defined. Most mortality-based studies have used selected populations with limited power or have restricted analysis to liver-related causes of death.[8–15]

We know of no one study that systematically examines the risk of all causes of death after hepatitis B or hepatitis C infection in a community-based setting. To provide precise estimates of the risk of death after infection, we investigated the incidence and excess risk of disease-specific and all cause mortality in a population of people diagnosed with hepatitis B and hepatitis C infection in New South Wales (NSW), Australia.

Methods

Data sources

We did a retrospective study, linking notified cases of hepatitis B and hepatitis C infection in NSW to the Australian National Death Index (NDI). Notification to the NSW Health Department Notifiable Diseases Database (NDD) of newly diagnosed hepatitis B and hepatitis C infection has been mandatory for laboratories since 1991.[16] The case definition for hepatitis B notification requires detection of hepatitis B surface antigen or hepatitis B DNA. The case definition for hepatitis C notification requires detection of anti-hepatitis C antibody or hepatitis C RNA. Date of notification, sex, date of birth, last name, first name, postcode of residence, and NDD registration number were extracted from the database for people notified with hepatitis B or hepatitis C infection between Jan 1, 1990, and Dec 31, 2002.

The NDI database contains records of all deaths in Australia since 1980, based on reports from the Registrars of Births, Deaths, and Marriages in each State and Territory. Last name, first name, date of birth (or estimated year of birth), age at death, sex, date of death, ICD 9 (deaths before 1997) and ICD10 (deaths since 1997) classification code for underlying cause of death and NDI registration number were extracted from NDI for all notifications received by the end of 2002.

Linkage procedure

Record linkage between the NDD population and NDI was done in two steps: matching hepatitis B and hepatitis C notifications to identify co-infected cases, and matching NDD notifications to deaths in NDI. Linkage was done probabilistically on the basis of name, date of birth, sex, and place of residence data with Integrity software, version 3·6.[17]

Data linkage was done by NSW Health (NDD hepatitis B–NDD hepatitis C linkage) and the Australian Institute of Health and Welfare (NDD–NDI linkage). All

personal identifiers were removed before the linked data were transferred to the National Centre in HIV Epidemiology and Clinical Research for data analysis.

Statistical analysis

Causes of death in people with hepatitis B and hepatitis C infection were summarised as total counts of linked deaths. People who died within 6 months of hepatitis B or hepatitis C diagnosis were not included in analyses of the incidence of death because of the potential for bias towards higher rates of diagnosis in people with major morbidity. Incidence of death was determined by person-time methods. Person-years at risk were calculated for each person as time from date of NDD notification to either the date of death or Dec 31, 2002. For people with hepatitis B and hepatitis C co-infection, risk time commenced at the later of hepatitis B or hepatitis C notification.

For each cause of death, incidence seen in the study population was compared with the expected incidence derived from NSW population death rates by the calculation of standardised mortality ratios.[18,19] Ratios were adjusted by 5-year age-group, sex, and calendar year of hepatitis notification, with age-group and calendar year treated as time dependent covariates. People with missing information about age or sex on NDD notification were excluded from these analyses. CIs for standardised mortality ratios were estimated by use of a quadratic approximation, on the assumption that recorded deaths follow a Poisson distribution. Poisson regression was used to compare standardised mortality ratios, obtain p values, and test for change in slope. Causes of death were categorised according to ICD10 and corresponding ICD9 chapter headings. For drug related deaths, the Australian Bureau of Statistics classification was used, which included mental and behavioural disorders due to psychoactive substance use, misuse of non-dependence-producing substances, death by accidental, intentional, or undetermined intent, or poisoning or assault by drugs, medicaments, and biologicals.[20]

Ethics approval for the study was granted by NSW Health, NSW Cancer Council, the Australian Institute of Health and Welfare, and the University of New South Wales.

	Viral hepatitis notification		
	Hepatitis B virus n=39 109	Hepatitis C virus n=75 834	Hepatitis B and C co-infection n=2604
Year of viral hepatitis notification, median (IQR)	1997 (1994–2000)	1997 (1995–2000)	1999 (1996–2002)*
Age at viral hepatitis notification [years], median (IQR)	35 (27–44)	34 (28–41)	35 (29–42)*
Data missing [n], (%)	1507 (4%)†	789 (1%)	13 (<1%)
Males [n], (%)	20 808 (53%)	47 903 (63%)	1932 (74%)
Data missing [n], (%)	772 (2%)	555 (1%)	14 (1%)
Linked deaths‡ [n], (%)	1233 (3%)	4008 (5%)	186 (7%)

*At second infection. †84% received before 1993. ‡Includes deaths within 6 months of hepatitis notification.

Table 1: **Characteristics of people diagnosed with hepatitis B, hepatitis C, or co-infection in NSW 1990–2002**

	Description	Viral hepatitis notification											
		Hepatitis B virus				Hepatitis C virus				Hepatitis B and C co-infection			
		Observed deaths	Rate	SMR	95% CI	Observed deaths	Rate	SMR	95% CI	Observed deaths	Rate	SMR	95% CI
	All cause	896	46·1	1·4	1·3–1·5	2342	92·5	3·1	3·0–3·2	150	141·7	5·6	4·8–6·6
A00-B99	Infection	118	6·1	10·2	8·5–12·2	270	7·5	11·4	10·1–12·8	21	19·8	30·0	19·5–46·0
C00-D48	Neoplasms	326	16·8	1·6	1·5–1·8	518	14·3	1·8	1·6–1·9	24	22·7	3·2	2·2–4·8
D50-D89	Blood/immune	6	0·3	9·3	4·2–20·6	17	0·5	15·1	9·4–24·2	0			
E00-E90	Endocrine	41	2·1	2·3	1·7–3·1	88	2·4	2·9	2·4–3·6	2	1·9	2·7	0·7–10·7
F00-F99	Mental and behavioural	24	1·2	1·3	0·9–2·0	590	16·3	15·0	13·9–16·3	26	24·6	23·6	16·1–34·7
G00-G99	Nervous system	11	0·6	0·7	0·4–1·2	49	1·4	1·6	1·2–2·2	0			
I00-I99	Circulatory system	149	7·7	0·8	0·6–0·9	450	12·5	1·3	1·2–1·5	19	17·9	2·6	1·6–4·0
J00-J99	Respiratory system	27	1·4	0·6	0·4–0·9	84	2·3	1·2	1·0–1·5	2	1·9	1·3	0·3–5·3
K00-K-93	Digestive system	40	2·1	1·8	1·3–2·5	221	6·1	6·0	5·2–6·8	12	11·3	12·1	6·8–21·2
L00-L99	Skin	0				3	0·1	1·7	0·6–5·4	0			
M00-M99	Musculoskeletal	4	0·2	1·4	0·5–3·6	13	0·4	2·6	1·5–4·5	0			
N00-N99	Genitourinary	17	0·9	2·1	1·3–3·4	41	1·1	2·7	2·0–3·7	3	2·8	10·6	3·4–32·7
O00-Q99	Pregnancy/perinatal/ congenital	6	0·3	1·9	0·9–4·3	10	0·3	1·6	0·9–3·0	0			
R00-R99†	Other	4	0·2	2·0	0·8–5·4	38	1·1	9·5	6·9–13·0	1	0·9	9·1	1·3–64·8
V00-Y98	External	123	6·3	1·5	1·3–1·8	950	26·3	5·5	5·2–5·9	40	37·8	7·2	5·3–9·8

Rate reported per 10 000 person years. SMR=standardised mortality ratio, adjusted for age, sex, and calendar year. Death, rate, and SMR calculated only including hepatitis cases where death occurred at least 6 months after hepatitis diagnosis and information about age at diagnosis and sex were available. *For deaths before 1997, corresponding ICD9 codes were used. †Includes deaths with no cause specified.

Table 2: **Causes of death in people diagnosed with hepatitis B, hepatitis C, or hepatitis B and C co-infection in NSW 1990–2002 by ICD-10 code***

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 120 815 hepatitis B and hepatitis C infections were notified to the NDD from 1990 to 2002. The data linkage processes identified 664 duplicate records and 2604 people with both hepatitis C and hepatitis B notifications to give a final study population of 117 547. From this population, three groups were defined on the basis of hepatitis B and hepatitis C infection status (table 1). The three groups were similar in their median year and age at NDD notification; the hepatitis B and hepatitis C co-infected group had a higher proportion of men. The number of deaths identified in the study population were 1233 (3·2%) for hepatitis B, 4008 (5·3%) for hepatitis C and 186 (7·1%) for hepatitis B and hepatitis C co-infection. The most frequently reported causes of death were neoplasms for hepatitis B (469 [38%] of 1233), and external causes for hepatitis C (1108 [28%] of 4008) and hepatitis B and hepatitis C co-infection (50 [27%] of 186).

A fifth to a quarter of deaths took place within 6 months of diagnosis of hepatitis (hepatitis B 27%, hepatitis C 17%, hepatitis B and C 19%). After exclusion of these cases, the hepatitis B, hepatitis C, and co-infected groups

	Description	Sex	Viral hepatitis notification											
			Hepatitis B				Hepatitis C				Hepatitis B and C co-infection			
			Observed deaths	Rate	SMR	95% CI	Observed deaths	Rate	SMR	95%CI	Observed deaths	Rate	SMR	95% CI
	All liver related		227	11·7	12·2	10·7–13·9	503	13·9	16·8	15·4–18·3	31	29·3	32·9	23·1–46·7
		Men	192	18·5	13·0	11·3–14·9	363	16·2	15·1	13·6–16·7	25	31·4	29·4	19·9–43·5
		Women	35	3·9	9·3	6·6–12·9	140	10·2	23·9	20·3–28·2	6	22·9	64·2	28·8–143
B15–B19†	Viral hepatitis		34	1·8	37·6	26·8–52·6	90	2·5	50·5	41·1–62·1	6	5·7	107·8	48·4–240
		Men	27	2·6	36·4	24·9–53·0	61	2·7	40·2	31·3–51·6	6	7·5	115·5	51·9–257
		Women	7	0·8	43·0	20·5–90·2	29	2·1	110·1	76·5–159	0			
B942†	Sequelae of viral hepatitis		31	1·6	34·2	24·0–48·6	110	3·0	57·3	47·5–69·1	8	7·6	118·6	59·3–237
		Men	26	2·5	35·0	23·9–51·5	78	3·5	47·5	38·1–59·4	6	7·5	96·7	43·4–215
		Women	5	0·6	30·2	12·6–72·6	32	2·3	114·8	81·2–162	2	7·6	370·4	92·6–1481
C22†	Liver cancer		131	6·7	27·8	23·4–33·0	117	3·2	16·7	14·0–20·1	8	7·6	39·7	19·9–79·5
		Men	110	10·6	29·6	24·6–35·7	83	3·7	15·4	12·4–19·1	7	8·8	39·2	18·7–82·2
		Women	21	2·3	21·0	13·7–32·3	34	2·5	21·2	15·1–29·6	1	3·8	43·9	6·2–312
K70†	Alcoholic liver disease		16	0·8	2·1	1·3–3·4	96	2·7	7·9	6·5–9·6	4	3·8	9·8	3·7–26·1
		Men	16	1·5	2·6	1·6–4·2	73	3·3	7·2	5·8–9·1	2	2·5	5·4	1·4–21·6
		Women	0				23	1·7	11·0	7·3–16·6	2	7·6	52·3	13·1–209
K71–K77†	Non-alcoholic liver disease		15	0·8	3·4	2·0–5·6	90	2·5	12·7	10·4–15·6	5	4·7	23·7	9·9–56·9
		Men	13	1·3	3·8	2·2–6·6	68	3·0	12·5	9·8–15·8	4	5·0	21·3	8·0–56·8
		Women	2	0·2	1·9	0·5–7·7	22	1·6	13·6	9·0–20·7	1	3·8	42·8	6·0–304
B20–B24	HIV		35	1·8	9·2	6·6–12·9	49	1·4	5·2	4·0–6·9	6	5·7	18·3	8·2–40·8
		Men	33	3·2	9·1	6·5–12·8	46	2·0	5·1	3·8–6·8	6	7·5	18·6	8·4–41·5
		Women	2	0·2	12·9	3·2–51·6	3	0·2	11·8	3·8–36·6	0			
C81–C96	Lymphoid		35	1·8	1·7	1·2–2·4	62	1·7	1·9	1·5–2·5	2	1·9	2·4	0·6–9·6
		Men	22	2·1	1·6	1·0–2·4	40	1·8	1·9	1·4–2·5	2	2·5	2·9	0·7–11·6
		Women	13	1·4	2·0	1·2–3·5	22	1·6	2·1	1·4–3·2	0			
ABS	Drug related		31	1·6	1·4	1·0–2·0	989	27·4	19·3	18·1–20·5	41	38·7	24·7	18·2–33·5
		Men	26	2·5	1·6	1·1–2·3	759	33·8	17·7	16·5–19·0	37	46·4	24·6	17·8–34·0
		Women	5	0·6	0·9	0·4–2·2	230	16·8	27·6	24·2–31·4	4	15·3	25·3	9·5–67·4

Total=all linked deaths. Rate reported per 10 000 person years. SMR=standardised mortality ratio, adjusted for age, sex, and calendar year. Deaths, rate, and SMR calculated only including hepatitis cases where death occurred at least 6 months after hepatitis diagnosis and information about age at diagnosis and sex were available. ABS=Australian Bureau of Statistics definition of drug related deaths, includes ICD 10 codes of: F11-F16, F19, F55, X40–X44, X60–X64,X85, Y10–Y14 and corresponding ICD9 codes. *For deaths before 1997, corresponding ICD9 codes were used. †Consist of "All liver related".

Table 3: **Causes of death related to viral hepatitis in NSW 1990–2002 by ICD-10 code**

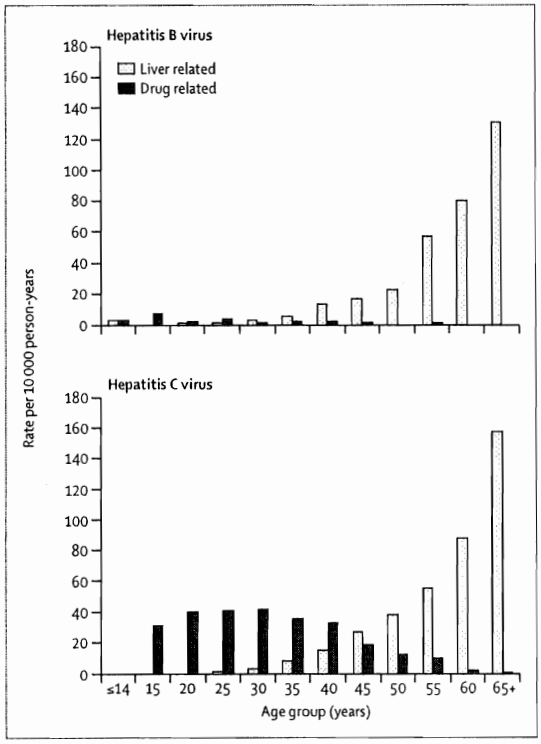

Figure 1: Incidence of liver related and drug related deaths by age group and type of viral hepatitis

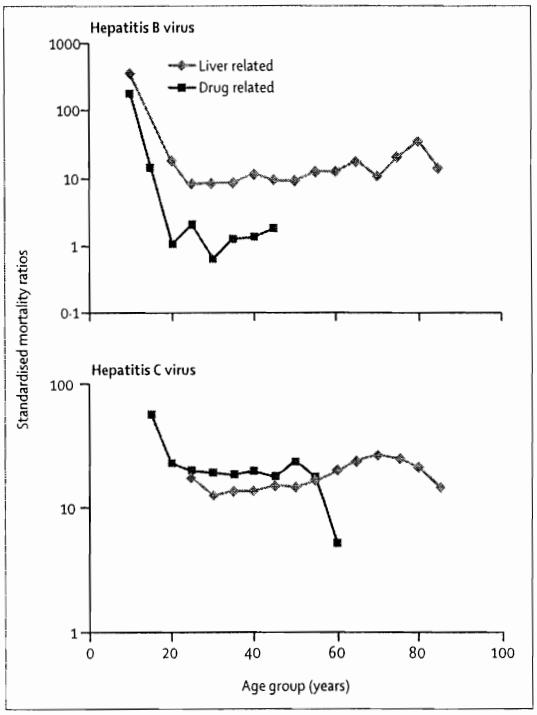

Figure 2: Standardised mortality ratios for liver-related and drug-related deaths by age group and type of viral hepatitis

contributed a median of 5·3, 4·6, and 3·5 years of follow-up per person, respectively.

The incidence of death and standardised mortality ratios comparing mortality in the hepatitis-diagnosed population with the general population of NSW, for all causes of death, are shown in table 2. The overall incidence of death was greatest for people with hepatitis B and C co-infection, followed by hepatitis C, and hepatitis B (141·7, 92·5, and 46·1 deaths per 10 000 person-years, respectively). Standardised mortality ratios for all cause mortality were significantly raised in all three groups and showed the same relation as incidence with type of hepatitis (standardised mortality ratios 5·6, 3·1, and 1·4, respectively).

Liver related mortality in all three hepatitis groups was 12 to 33 times greater than in the NSW population (table 3). The comparative risk was greatest for people with co-infection (standardised mortality ratios 32·9, 95% CI 23·1–46·7) followed by those with hepatitis C (16·8, 15·4–18·3) and hepatitis B (12·2, 10·7–13·9) mono-infections. Although the incidence of liver-related death was higher for men than women with hepatitis C (16·2 *vs* 10·2 deaths per 10 000 person-years), women had a higher standardised mortality ratio than men (23·9, 20·3–28·2 *vs* 15·1, 13·6–16·7). The relation between age and liver-related death was similar across hepatitis groups with low mortality rates below the age of 30–40 years, followed by an exponential rise in mortality rate with increasing age at risk (figure 1). Standardised mortality ratios for hepatitis B and hepatitis C liver-related mortality increased over the 50–70-year age-groups (figure 2).

Hepatocellular carcinoma accounted for more liver related deaths than any other liver-related diagnostic code in the hepatitis B group (131 [58%] of 227). The risk of death from hepatocellular carcinoma in all hepatitis groups was significantly raised, but was significantly lower in the hepatitis C infected group (standardised mortality ratios 16·7, 95% CI 14·0–20·1) than either the hepatitis B (standardised mortality ratios 27·8, p<0·0001) or hepatitis B and C co-infected groups (39·7, p=0·017; table 3). Death coded as viral hepatitis and sequelae accounted for the greatest excess mortality in all hepatitis infection groups with standardised mortality ratios of around 36, 48, and 113 in the hepatitis B, hepatitis C and hepatitis B and C co-infected groups, respectively (table 3).

Excess risk of death from alcohol-related liver disease in those with hepatitis C and those with hepatitis B and C co-infection was three to four times greater than for the hepatitis B infection group (table 3). The association between sex and alcohol-related liver disease differed across the three infection groups: women were at greater excess risk in the hepatitis B and C co-infected group (p=0·026); at increased excess risk, though not significantly, in the hepatitis C group (p=0·079); and in

the hepatitis B group all deaths from alcohol-related liver disease were in men.

The risk of drug-related death was marginally raised in people with hepatitis B infection (standardised mortality ratio 1·4, 95% CI 1·0–2·0) but markedly raised in people with hepatitis C (19·3, 18·1–20·5) and with hepatitis B and C co-infection (24·7, 18·2–33·5) compared with the NSW population. The excess in hepatitis C drug-related deaths was significantly greater than for liver-related deaths (p=0·012), as was the absolute rate for drug-related deaths (27 per 10 000 person-years, 95% CI 26–29) compared with liver-related death (14 per 10 000 person-years, 13–15).

The age distribution of drug-related deaths was similar between the hepatitis C and the co-infected groups and markedly different from the distribution of liver-related deaths (figure 1, co-infection data not shown). In these two infection groups, drug-related deaths were predominant in age groups between 15 and 40 years. Women were at greater risk of excess drug-related death than men only in the hepatitis C group (table 3). Standardised mortality ratios for women were consistently greater than for men 15–44 years of age (figure 3). The greatest difference between sexes was at younger ages, and was statistically different for people between 15 and 24 years of age (men 17·1, 21·4–23·0; women 56·9, 39·2–79·9; p<0·0001).

Over time, in those with hepatitis C infection, the rate of drug-related death was constant at 35–43 deaths per 10 000 person-years between 1995 and 1999, and dropped significantly to 27 per 10 000 person-years in 2000–02 (p<0·0001). Liver and non-liver non-drug-related death rates remained constant between 1995 and 2001, and fell slightly in 2002 (figure 4). Standardised mortality ratios for liver and drug related deaths declined slightly from 1995 to 2002 (figure 5). The number of liver-related deaths linked to hepatitis C rose from ten in 1993 to 81 in 2001.

Standardised mortality ratios for deaths that were not drug related or liver related were marginally though significantly raised for hepatitis B (1·1, 1·0–1·2), and significantly raised for the hepatitis C (1·9, 1·8–2·0) and the co-infected groups (3·2, 2·6–4·0). Standardised mortality ratios for deaths other than HIV (1·4, 1·3–1·5), alcohol-related liver disease (2·2, 2·1–2·3), and drug-related death (4·1, 3·3–4·9) also remained significantly raised.

Raised standardised mortality ratios for infection-related mortality (table 2) could be attributed mainly to viral hepatitis and also to HIV-related death (table 3). Excess HIV mortality was significantly greater in the hepatitis B and co-infected groups (p=0·01) than in the hepatitis C mono-infected group (p=0·004). Excess mortality from neoplasms (table 2) could mainly be accounted for by hepatocellular carcinoma in the hepatitis B infection group (standardised mortality ratio neoplasms excluding hepatocellular carcinoma were 1·0, 95% CI 0·9–1·2), but was also contributed to by lymphoid malignancies in all hepatitis groups (table 3), partly attributed by malignancies of uncertain origin in the hepatitis C and co-infected groups (3·6, 2·4–5·4 and 7·4, 1·0–52·5), and attributed by lung cancer in the hepatitis C infected group (1·5, 1·2–1·9). Excess mortality from blood and immune disorders was evident for the hepatitis B and hepatitis C groups (9·3, 4·2–20·6 and 15·1, 9·4–24·2); all causes of death were for chronic conditions that could have required transfusion of blood products, apart from 2 of 17 within the hepatitis C group. Excess mortality for mental and behavioural reasons was evident in the hepatitis C and co-infected groups (15·0, 13·9–16·3 and 23·6 16·1–34·7), and 488 (93%) of 590 and 23 (88%) of 26 of these deaths, respectively, were coded as resulting from drug dependence.

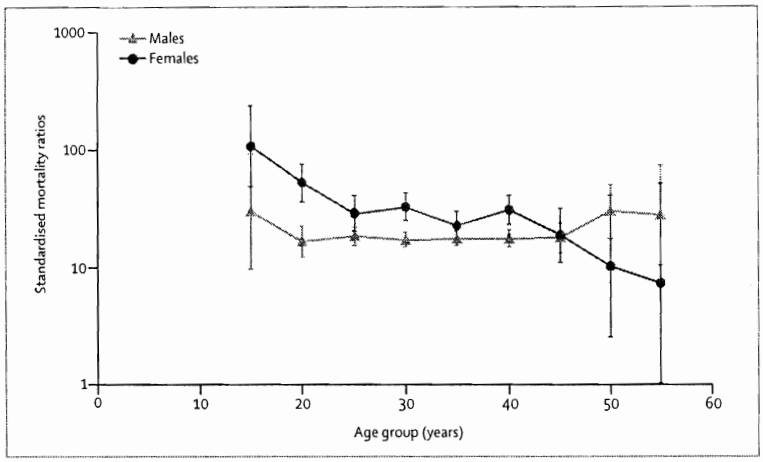

Figure 3: Standardised mortality ratios for drug-related death by age group and sex in people diagnosed with hepatitis C infection
Bars=95% CI.

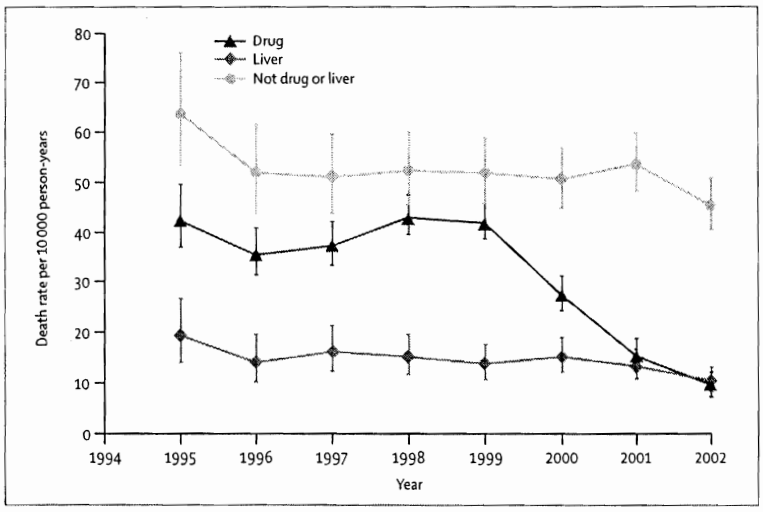

Figure 4: Death rate by cause and year in people diagnosed with hepatitis C infection
Bars=95% CI.

Discussion

In this large-scale study of liver disease-related mortality and all cause mortality in people diagnosed with community acquired hepatitis B and hepatitis C infection, the overall mortality rate was around one and a half to five times greater than the standard population, with the greatest excess in people diagnosed with hepatitis B and C co-infection. The main cause of hepatitis B deaths was liver related, particularly hepatocellular carcinoma, whereas in the hepatitis C and the co-infection groups drug-related deaths were most frequent. The excess risk of drug related death in people with hepatitis C was significantly greater for women than men, particularly in younger age groups.

Divergent results have been reported in other cohort studies regarding the relation between all cause mortality and hepatitis B and hepatitis C infection. Hepatitis B studies from China report a three times greater risk of death,[10,21] and a hospital based Italian study reports a five fold increased risk.[9] Studies of community acquired hepatitis C infection in random or population based samples have shown significantly increased risks of death of a similar magnitude to the three times increased risk detected in our study.[22,23] However, other hepatitis B and hepatitis C studies, done in selected populations such as transfusion recipients, hospital based cohorts, and military recruits, have reported no significantly increased risk of all cause mortality.[8,11–15]

The associations between hepatitis B, hepatitis C, and co-infection, liver related mortality, particularly hepatocellular carcinoma, have been frequently reported in previous studies and are consistent with the findings in our study.[8,21–26] The age distribution of liver-related deaths was similar across the three infection groups in our study and indicates the generally slow rate of progression from infection to severe liver disease for both hepatitis B and hepatitis C infection. The rate of liver-related death from diagnosis in the mono-infected groups is also indicative of a slow progression and low individual risk of liver disease for those with community acquired infection. However, relative mortality rates were higher in those 50 to 70 years of age, which suggested faster disease progression in older infected people. The standardised mortality ratio for hepatocellular carcinoma was noticeably higher in women than men for hepatitis C, but not hepatitis B. Being of southeast Asian background is a common risk factor for hepatitis B acquisition in Australia,[27] and is thought to be associated with low alcohol use. Conversely, hepatitis C infection in Australia is largely through intravenous drug use, which is also associated with high alcohol use, as illustrated by the higher standardised mortality ratios for deaths from alcohol-related liver disease in the hepatitis C groups.[28,29] Therefore, the higher standardised mortality ratios for hepatocellular carcinoma in women than men with hepatitis C, but not hepatitis B, might be related to differing alcohol use in these populations.

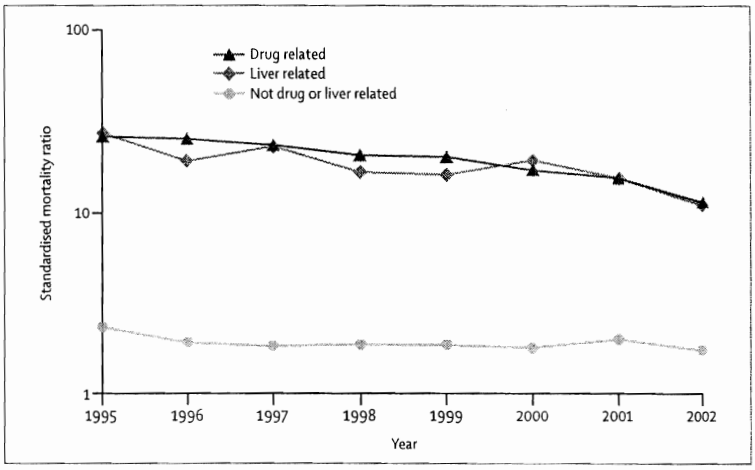

Figure 5: Standardised mortality ratios by cause and year in people diagnosed with hepatitis C infection

The drug-related mortality in people with hepatitis B and hepatitis C in our study is consistent with the known epidemiology of these two blood-borne viruses in Australia. The estimated proportion of infection acquired by intravenous drug use in Australia is 5% for hepatitis B and 80% for hepatitis C, respectively.[27,28,30] The relation between suicide, accidental or drug related deaths, and hepatitis C has been previously noted, but raised risks of between 5 and 10 in other studies[12,23] are significantly lower than our study. Factors such as age, hepatitis C risk group distribution, and the study setting are likely to influence these mortality risks. A hospital-based setting that included older individuals with later stages of liver disease is unlikely to include many people still at risk of drug-related death. Similarly, populations where intravenous drug use is not the main risk factor for transmission, such as in transfusion-acquired populations, are unlikely to find associations with drug related deaths. Further, causes of death in this study have been categorised to specifically capture drug-related death.

The relation between hepatitis C infection and drug-related mortality by age and sex are similar to those of a cohort study in Scotland on intravenous drug use that detected the highest excess risk of mortality in young female drug users.[31] The higher standardised mortality ratios for young women than for men in our study could be explained by the rarity of drug-related death in young women without hepatitis C infection. The relation between hepatitis C, intravenous drug use and drug-related death in NSW is also manifest in reduction in drug-related death in our study from 2000 onwards. This trend probably mirrors the dramatic reduction in the availability of heroin and substantial reduction in the number of heroin overdoses during this time in NSW.[32,33] The only marginal reduction in drug-related standardised mortality ratios over time is likely to indicate coinciding reduction in the background rate of drug-related death. Future mortality trends, including distribution of deaths

and causes of death, will depend on rates of intravenous drug use in people with hepatitis C, liver disease stage distribution, and the potential effect of treatment in the hepatitis C population. The rapid escalation of the hepatitis C epidemic in Australia during the 1990s means that a large proportion of the hepatitis C population have early liver disease.

The study population was derived from the state notifications database and is largely representative of the infected populations (especially for hepatitis C infections) in Australia. An estimated 70–80% of hepatitis C and 60% of hepatitis B prevalent chronic infections have been diagnosed and reported to notification systems in Australia.[27,28,34,35] The high proportion of diagnosed cases relates to high rates of hepatitis B and hepatitis C screening in at-risk populations in Australia. For example, surveys of intravenous drug users attending needle and syringe programs indicate that 60–70% have been tested for hepatitis C in the previous 12 months.[32] The undiagnosed population is probably at lower risk of drug-related or liver-related death, and only a true population-based random sample study could accurately estimate risk for all exposed people.

There is a large burden of hepatitis B and hepatitis C in developing countries, especially in parts of Asia and Africa.[36,37] Generalisation of our study findings to these countries is problematic because of the differences in the underlying cause of infection, particularly the association between intravenous drug use and hepatitis C in our study. Further, in developing countries competing mortality risks might differ considerably. Therefore, there is a need for similar community-based studies in developing countries.

Our study has several limitations. The study population included cases of notified acute hepatitis B infection and acute hepatitis C infection, although these cases represented less than 2% of total notifications. Additionally, notification of hepatitis C is based on anti-hepatitis C antibody rather than hepatitis C RNA detection. According to a review of hepatitis C clearance studies, an estimated 25% of notifications would represent people who have spontaneously cleared infection.[38] Thus, standardised mortality ratios for causes of death directly related to hepatitis C infection could be underestimated by as much as 25%. The number of cases of hepatitis C treatment related clearance would be small, since fewer than 1000 people per year were treated in NSW during the study, and treatment response rates have only improved in recent years.[30] The number of people with chronic hepatitis B who receive antiviral therapy has also been low in Australia. Because date of infection was unknown, risk in this study pertains to risk from date of diagnosis and is likely to overestimate risk of death from time of infection. Median age at time of hepatitis C infection is estimated to be 20–25 years, whereas the median age at notification in the study population was 34 years.[28] Time from hepatitis C infection to cirrhosis is protracted, often more than 30 years with more severe liver-related outcomes taking even longer to become evident.[14,39] Further, the results of this study describe outcomes soon, within 10 to 12 years, after diagnosis of infection. Standardised mortality ratios might also have been slightly underestimated because of people migrating and dying overseas.

Information about source of infection and country of birth were not available from the notification data. This omission is of particular concern with regard to hepatitis B associated mortality because of the estimated high proportion of non-Australian born cases.[27] Further we did not have information about hepatitis delta virus co-infection, which increases the risk of hepatocellular carcinoma, in people with hepatitis B infection. The higher mortality ratios related to HIV in the hepatitis B than the hepatitis C group is likely to result from a higher prevalence of HIV co-infection in people with hepatitis B. The prevalence of HIV in people with hepatitis C is low because of limited HIV transmission through intravenous drug use in Australia.[28] These issues highlight the limitation of identifying deaths through the death registry without access to hospital records and information about underlying conditions and risk factors. Further the sensitivity and specificity of data linkage in this study is unknown and likely to be less than 100%.

We show a high excess mortality risk associated with hepatitis B and hepatitis C infection and liver disease, particularly hepatocellular carcinoma. The effects of hepatitis B and hepatitis C treatment on infection-related mortality are yet to be seen. Mortality risk associated with drug use in people with hepatitis C was high, especially for young people. Our data highlight the need for dual strategies for reduction of morbidity and mortality related to hepatitis C: a focus on reduction of drug-related harm for young groups and on reduction of liver disease progression in older groups.

Contributors

J Amin contributed to the study design, the acquisition, analysis, and interpretation of data, and drafting the article. M Law and G Dore contributed to the study conception, design, and the interpretation of data; M Bartlett contributed to the acquisition of data; J Kaldor contributed to study conception and design. All authors revised and approved the final version for publication.

Conflict of interest statement

We declare that we have no conflict of interest.

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HEPATITIS B e ANTIGEN AND THE RISK OF HEPATOCELLULAR CARCINOMA

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ABSTRACT

Background The presence of hepatitis B e antigen (HBeAg) in serum indicates active viral replication in hepatocytes. HBeAg is thus a surrogate marker for the presence of hepatitis B virus DNA. We conducted a prospective study to determine the relation between positivity for hepatitis B surface antigen (HBsAg) and HBeAg and the development of hepatocellular carcinoma.

Methods In 1991 and 1992, we enrolled 11,893 men without evidence of hepatocellular carcinoma (age range, 30 to 65 years) from seven townships in Taiwan. Serum samples obtained at the time of enrollment were tested for HBsAg and HBeAg by radioimmunoassay. The diagnosis of hepatocellular carcinoma was ascertained through data linkage with the computerized National Cancer Registry in Taiwan and with death certificates. We performed a multiple regression analysis to determine the relative risk of hepatocellular carcinoma among men who were positive for HBsAg alone or for HBsAg and HBeAg, as compared with those who were negative for both.

Results There were 111 cases of newly diagnosed hepatocellular carcinoma during 92,359 person-years of follow-up. The incidence rate of hepatocellular carcinoma was 1169 cases per 100,000 person-years among men who were positive for both HBsAg and HBeAg, 324 per 100,000 person-years for those who were positive for HBsAg only, and 39 per 100,000 person-years for those who were negative for both. After adjustment for age, sex, the presence or absence of antibodies against hepatitis C virus, cigarette-smoking status, and use or nonuse of alcohol, the relative risk of hepatocellular carcinoma was 9.6 (95 percent confidence interval, 6.0 to 15.2) among men who were positive for HBsAg alone and 60.2 (95 percent confidence interval, 35.5 to 102.1) among those who were positive for both HBsAg and HBeAg, as compared with men who were negative for both.

Conclusions Positivity for HBeAg is associated with an increased risk of hepatocellular carcinoma. (N Engl J Med 2002;347:168-74.)

CHRONIC hepatitis B virus (HBV) infection is a serious clinical problem because of its worldwide distribution and potential for adverse sequelae, including hepatic cirrhosis and hepatocellular carcinoma. It is particularly prevalent in the Asian–Pacific region, where patients usually acquire the infection at the time of birth or in early childhood.

The natural course of chronic HBV infection acquired early in life can be divided into three phases.[1,2] The first phase is characterized by active replication of HBV, positivity for hepatitis B e antigen (HBeAg), and normal-to-low levels of serum aspartate aminotransferase and alanine aminotransferase. The second phase, characterized by immune clearance, usually occurs from the age of 15 to 35 years, during which hepatitis flares may occur as the result of specific, T-lymphocyte–mediated cellular responses to viral antigens and apoptosis of hepatocytes. This phase subsides as viral replication declines, with the appearance of antibodies against HBeAg and clinical remission. In the third, or residual, phase, patients are positive for hepatitis B surface antigen (HBsAg) and negative for HBeAg, and they do not have active liver disease.[1,2] Epidemiologic studies have shown that positivity for HBsAg is one of the most important risk factors for hepatocellular carcinoma.[3-5]

Positivity for HBeAg usually indicates active replication of HBV. Loss of detectable HBeAg, together with the emergence of antibodies against HBeAg, has been used as a key end point in studies of the efficacy of various agents, including lamivudine and interferon, for the treatment of chronic hepatitis B.[6,7] However, the role of positivity for HBeAg in the prediction of hepatocellular carcinoma remains inconclusive. Various studies of case series have found that the prevalence of HBeAg was lowest among patients with hepatocel-

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lular carcinoma, highest among patients with chronic hepatitis B, and intermediate among those with liver cirrhosis.[8,9] In several case–control studies, however, the prevalence of HBeAg was significantly higher among HBsAg-positive patients with hepatocellular carcinoma than among matched HBsAg-positive controls.[10-14] All these studies were cross-sectional in design, with disease status and the prevalence of antigen positivity determined at the same time. The studies did not determine whether positivity for HBeAg preceded the onset of hepatocellular carcinoma. We conducted a prospective study of the relation between positivity for HBeAg and the risk of hepatocellular carcinoma among 11,893 men in Taiwan.

METHODS

Study Cohort

From 1991 to 1992, we invited all 47,079 men between the ages of 30 and 65 years who were living in seven townships in Taiwan to participate in the study; the men were contacted by mail. A total of 11,893 men (25 percent) agreed to participate. Each subject provided written informed consent for us to conduct an interview, collect a blood specimen, and perform various serologic and biochemical assays. The study was conducted between February 1991 and September 2000.

Data Collection and Blood Tests

All the men were interviewed in person with the use of a structured questionnaire administered by well-trained public health nurses. The men were questioned about sociodemographic characteristics, diet, cigarette smoking, consumption of alcohol, betel-nut chewing, their medical and surgical history, and any family history of hepatocellular carcinoma or liver cirrhosis. A 10-ml specimen of blood was collected with the use of a disposable vacuum syringe. Samples of serum separated on the day of blood collection were kept in a freezer (at −70°C) until they were assayed. The specimens were tested at the time of enrollment for HBsAg and HBeAg by radioimmunoassay with the use of a commercial kit (Abbott Laboratories) and were tested for antibodies against hepatitis C virus by enzyme immunoassay with the use of a second-generation commercial kit (Abbott Laboratories).

For men in whom hepatocellular carcinoma was diagnosed during follow-up who were positive for HBsAg and negative for HBeAg at enrollment, tests for antibodies against HBeAg and HBV DNA in serum samples obtained at the time of enrollment were performed in 2002 as part of a nested case–control substudy. For each man with hepatocellular carcinoma, we identified two healthy controls matched for age, date of enrollment, and township, except that for each of two men with hepatocellular carcinoma, there was only one matched control for whom frozen serum samples were available. Thus, frozen serum samples collected at the time of enrollment were available for a total of 44 men with hepatocellular carcinoma and 86 matched controls who were positive for HBsAg and negative for HBeAg. These samples were tested for antibodies against HBeAg with the use of an enzyme-linked immunoassay (Abbott Laboratories) and were tested for HBV DNA with the use of a branched-chain DNA assay (Quantiplex, Chiron), according to the manufacturer's instructions. The threshold of detection for the quantitative assay of DNA was 2.5 pg per milliliter.

Follow-up for Hepatocellular Carcinoma

In Taiwan, interferon, lamivudine, or other antiviral or immune therapy was rarely used to treat chronic hepatitis B before 2001. The Bureau of National Health Insurance in Taiwan did not provide reimbursement for the cost of treatment with lamivudine until March 2001. Since treatment with interferon alfa is expensive and has severe side effects that make it difficult to tolerate, the Bureau of National Health Insurance only recently began to provide reimbursement for the cost of this treatment. Other antiviral or immune therapies are also rarely used to treat chronic hepatitis B in Taiwan. For these reasons, we did not refer our subjects with chronic hepatitis B to the hospital for treatment after enrollment.

At the time of enrollment, none of the men had known hepatocellular carcinoma on the basis of screening tests (abdominal ultrasonography and serologic tests), interviews, and the absence of linkage with the National Cancer Registry. Cases of hepatocellular carcinoma were ascertained by computerized linkage of data with information from the National Cancer Registry in Taiwan for the period from January 1, 1984, through September 30, 2000. In addition, we linked data with information from death certificates to identify deaths from cases of hepatocellular carcinoma that were not included in the National Cancer Registry. The diagnosis was based on pathological examination in 56 men and on the results of abdominal ultrasonographic, angiographic, or computed tomographic studies combined with an elevated serum alpha-fetoprotein level (≥400 ng per milliliter) in 55 men.[10-13]

Statistical Analysis

The person-years of follow-up for each subject were calculated from the date of enrollment to the date of the diagnosis of newly developed hepatocellular carcinoma, the date of death, or the date of the last link to data from the National Cancer Registry (September 30, 2000), whichever came first. Incidence rates were calculated by dividing the number of incident cases of hepatocellular carcinoma by the number of person-years of follow-up. Data for men in whom hepatocellular carcinoma was not diagnosed were censored at the date of death or the last date of follow-up (September 30, 2000). A Cox's proportional-hazards model was used to estimate the relative risk of hepatocellular carcinoma associated with positivity for HBsAg and HBeAg and other risk factors, including advanced age, positivity for antibodies against hepatitis C virus, cigarette smoking, and consumption of alcohol. The 95 percent confidence intervals for the relative risks were also calculated. Significance levels were determined with the use of two-tailed tests. The cumulative incidence of hepatocellular carcinoma was calculated for men who were negative for both HBsAg and HBeAg, those who were positive for HBsAg alone, and those who were positive for both HBsAg and HBeAg, with the use of the Nelson–Aalen method (a nonparametric method for estimating the cumulative hazard).[15-17] For the 130 men included in the nested case–control substudy described above, we used logistic-regression analysis to determine the association between the level of HBV DNA and hepatocellular carcinoma. Statistical analysis was performed with Stata software (Stata).

RESULTS

The prevalence of HBsAg among all men and the prevalence of HBeAg among those who were positive for HBsAg are shown in Table 1 according to age, cigarette-smoking status, and use or nonuse of alcohol. The older the age, the lower the prevalence of HBsAg and HBeAg. The prevalence was consistent with the rates reported previously in Taiwan.[1,2] Thus, we considered the study cohort to be representative of the general population of Taiwanese men in terms of the prevalence of HBsAg and HBeAg.

Men who smoked and those who drank alcohol had a lower prevalence of HBsAg alone but a higher prevalence of HBeAg among those who were positive for HBsAg than did nonsmokers and nondrinkers. But

TABLE 1. PREVALENCE OF HEPATITIS B SURFACE ANTIGEN (HBsAg) AND HEPATITIS B e ANTIGEN (HBeAg) IN 11,893 MEN IN TAIWAN.

VARIABLE	NO. OF MEN	PREVALENCE OF HBsAg	P VALUE	PREVALENCE OF HBeAg AMONG HBsAg-POSITIVE MEN	P VALUE
		no. (%)		no. (%)	
Age at enrollment			<0.001*		<0.001*
30–39 yr	3242	771 (23.8)		180 (23.3)	
40–49 yr	2921	639 (21.9)		104 (16.3)	
50–59 yr	3684	695 (18.9)		72 (10.4)	
≥60 yr	2046	256 (12.5)		14 (5.5)	
Cigarette smoking†			0.004		0.80
No	5167	1088 (21.1)		168 (15.4)	
Yes	6713	1271 (18.9)		201 (15.8)	
Alcohol consumption‡			0.09		0.29
No	9434	1902 (20.2)		289 (15.2)	
Yes	2432	453 (18.6)		78 (17.2)	

*P values are based on a test for trend.

†Data were not available for 13 men.

‡Data were not available for 27 men.

the difference was statistically significant only for the prevalence of HBsAg alone among cigarette smokers and nonsmokers. Age and cigarette-smoking status differed significantly among the men who were negative for both HBsAg and HBeAg, those who were positive only for HBsAg, and those who were positive for both HBsAg and HBeAg ($P<0.001$ and $P=0.02$, respectively). The rates of use and nonuse of alcohol were similar in the three groups of men ($P=0.14$).

A total of 111 cases of hepatocellular carcinoma were diagnosed during a follow-up period of 92,359 person-years; the overall incidence rate was 120.2 cases per 100,000 person-years. The incidence rate was 39.1 among men who were negative for both HBsAg and HBeAg, 324.3 among those who were positive only for HBsAg, and 1169.4 among those who were positive for both HBsAg and HBeAg (Table 2). The prevalence of HBeAg was 39 percent among the men who were positive for HBsAg. The cumulative incidence of hepatocellular carcinoma is shown in Figure 1 for the three groups. The men who were positive for both HBsAg and HBeAg had a much higher cumulative incidence of hepatocellular carcinoma than those who were positive only for HBsAg and an even higher incidence than those who were negative for both ($P<0.001$ for both comparisons). The longer the follow-up, the greater the differences among the three groups.

Table 3 shows the results of the multiple-regression analysis with the use of the Cox proportional-hazards model. After adjustment for other risk factors, the relative risk of hepatocellular carcinoma was 9.6 (95 percent confidence interval, 6.0 to 15.2) for men who were positive for HBsAg alone and 60.2 (95 percent confidence interval, 35.5 to 102.1) for those who were positive for both HBsAg and HBeAg, as compared with men who were negative for both. An older age at the time of enrollment, the presence of antibodies against hepatitis C virus, cigarette smoking, and consumption of alcohol were also associated with an increased risk of hepatocellular carcinoma. The findings were similar when the data were stratified according to age, cigarette-smoking status, and use or nonuse of alcohol, in an analysis adjusted for other risk factors (Table 4).

In the nested case–control analysis that involved 130 men who were positive for HBsAg and negative for HBeAg (44 men with newly diagnosed hepatocellular carcinoma and 86 matched controls), 120 men (92 percent) were positive for antibodies against HBeAg, and 29 (22 percent) were positive for HBV DNA. The proportion of men who were positive for antibodies against HBeAg did not differ significantly between men with hepatocellular carcinoma and controls ($P=0.16$). Seventeen men with hepatocellular carcinoma (39 percent) and 12 controls (14 percent) had detectable serum levels of HBV DNA (>2.5 pg per milliliter). The odds ratio for the development of hepatocellular carcinoma was 3.9 (95 percent confidence interval, 1.6 to 9.2) for men who had detectable HBV DNA, as compared with those who had undetectable levels. The odds ratio increased with increases in the level of HBV DNA (Table 5).

DISCUSSION

It has been reported that in most patients with hepatocellular carcinoma, the disease develops after the

TABLE 2. INCIDENCE OF HEPATOCELLULAR CARCINOMA DURING FOLLOW-UP.*

RESULTS OF HBV ANTIGEN TESTS	PERSON-YR OF FOLLOW-UP	NO. OF MEN	NO. OF CASES OF HEPATOCELLULAR CARCINOMA	INCIDENCE RATE (95% CI)
				cases/100,000 person-yr
Negative for HBsAg and HBeAg	74,205	9532	29	39.1 (26.2–56.1)
Positive for HBsAg, negative for HBeAg	15,418	1991	50	324.3 (240.7–427.5)
Positive for HBsAg and HBeAg	2,736	370	32	1169.4 (799.9–1650.9)

*HBV denotes hepatitis B virus, CI confidence interval, HBsAg hepatitis B surface antigen, and HBeAg hepatitis B e antigen.

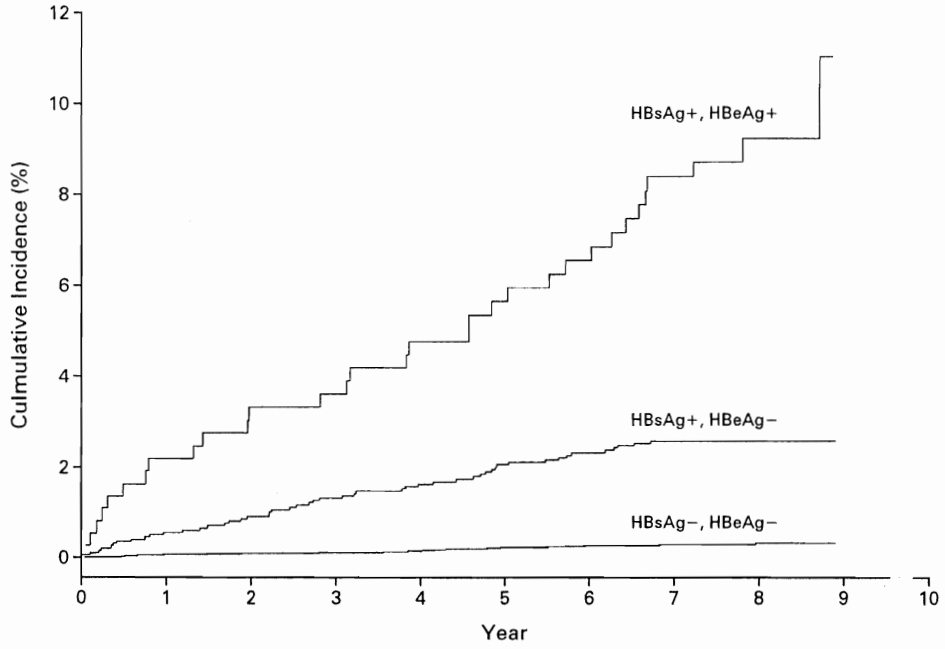

Figure 1. Cumulative Incidence of Hepatocellular Carcinoma during Follow-up among 11,893 Men in Taiwan, According to the Presence or Absence of Hepatitis B Surface Antigen (HBsAg) and Hepatitis B e Antigen (HBeAg) at Enrollment.
The cumulative incidence was estimated with the use of the Nelson–Aalen method.

development of antibodies against HBeAg.[18] In our follow-up study, with all blood samples collected and assayed before the diagnosis of hepatocellular carcinoma, the prevalence of HBeAg was 39 percent among men who were positive for HBsAg at the time of enrollment and who subsequently received a diagnosis of hepatocellular carcinoma — a much higher prevalence than that reported in a previous case-series study (18 percent)[9] and in previous case–control studies (22 and 25 percent).[12,14] Similarly, in our study, the relative risks of hepatocellular carcinoma among men who were positive for HBsAg alone (9.6) and among those who were positive for both HBsAg and HBeAg (60.2), as compared with men who were negative for both, were much higher than in previous case–control studies.[10-14]

TABLE 3. ADJUSTED RELATIVE RISK OF HEPATOCELLULAR CARCINOMA ACCORDING TO VARIOUS RISK FACTORS.*

VARIABLE	NO. OF CASES OF HEPATOCELLULAR CARCINOMA	ADJUSTED RELATIVE RISK (95% CI)
Age at enrollment		
30–39 yr†	6	1.0
40–49 yr	23	5.4 (2.2–13.2)‡
50–59 yr	55	13.5 (5.8–31.7)‡
≥60 yr	27	17.7 (7.1–43.9)‡
Results of HBV antigen tests		
Negative for HBsAg and HBeAg†	29	1.0
Positive for HBsAg, negative for HBeAg	50	9.6 (6.0–15.2)‡
Positive for HBsAg and HBeAg	32	60.2 (35.5–102.1)‡
Antibodies against hepatitis C virus		
No†	98	1.0
Yes	13	2.7 (1.5–4.9)‡
Cigarette smoking		
No†	41	1.0
Yes	70	1.5 (1.0–2.2)§
Alcohol consumption		
No†	80	1.0
Yes	31	1.5 (1.0–2.3)§

*Data were not available on cigarette smoking for 13 men, on alcohol consumption for 27, and on antibodies against hepatitis C virus for 77. CI denotes confidence interval, HBV hepatitis B virus, HBsAg hepatitis B surface antigen, and HBeAg hepatitis B e antigen.

†This was the reference group.

‡$P<0.001$.

§$P=0.06$.

Both indirect and direct carcinogenic mechanisms are involved in the pathogenesis of hepatocellular carcinoma induced by chronic HBV infection.[19] HBV may induce hepatocellular carcinoma indirectly by causing chronic necroinflammatory hepatic disease.[20] When HBV replication is sustained, as indicated by positivity for HBeAg, malignant transformation may occur as a result of continuous or recurrent cycles of hepatocyte necrosis and regeneration. The accelerated rate of cell turnover may act as a tumor promoter through the accumulation of spontaneous mutations or DNA damage caused by exogenous factors, resulting in an increased selective growth advantage for transformed cells. The accelerated turnover rate may also result in cleavage of viral DNA at specific motifs, resulting in linear DNA that is inserted into chromosomal DNA through increased intracellular topoisomerase I activity.[21] Chronic necroinflammation may induce malignant transformation by generating mutagenic reactive oxygen species during the inflammatory process.[22]

Active replication of HBV may also initiate malignant transformation through a direct carcinogenic mechanism by increasing the probability of insertion of viral DNA in or near proto-oncogenes, tumor-suppressor genes, or their regulatory elements of cellular DNA.[23,24] The integration of viral DNA may increase the production of transactivator protein hepatitis B X antigen, which may induce the malignant transfor-

TABLE 4. ADJUSTED RELATIVE RISK OF HEPATOCELLULAR CARCINOMA, WITH STRATIFICATION ACCORDING TO AGE, CIGARETTE-SMOKING STATUS, AND USE OR NONUSE OF ALCOHOL.

VARIABLE	ADJUSTED RELATIVE RISK (95% CI)*		
	NEGATIVE FOR HBsAg AND HBeAg	POSITIVE FOR HBsAg, NEGATIVE FOR HBeAg	POSITIVE FOR HBsAg AND HBeAg
Age at enrollment†			
≤55 yr	1.0	6.1 (3.3–11.4)	25.4 (13.3–48.6)
>55 yr	1.0	14.8 (7.5–29.5)	95.5 (42.5–214.5)
Cigarette smoking‡			
No	1.0	14.3 (6.1–33.8)	67.0 (26.1–171.7)
Yes	1.0	8.9 (5.1–15.5)	76.9 (39.4–150.3)
Alcohol consumption§			
No	1.0	9.7 (5.6–16.9)	69.0 (37.1–128.2)
Yes	1.0	11.4 (5.0–26.3)	52.1 (18.0–150.8)

*The reference group was the group of men who were negative for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). CI denotes confidence interval. $P<0.001$ for all comparisons.

†The analysis was adjusted for the presence or absence of antibodies against hepatitis C virus, cigarette-smoking status, and use or nonuse of alcohol.

‡The analysis was adjusted for age (as a continuous variable), the presence or absence of antibodies against hepatitis C virus, and use or nonuse of alcohol.

§The analysis was adjusted for age (as a continuous variable), the presence or absence of antibodies against hepatitis C virus, and cigarette-smoking status.